

Shedding Light on Vertebrate Magnetoreception

Minireview

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We review the challenges and recent progress in elucidating the physiological basis of animal magnetoreception. Behavioral and theoretical studies suggest a link between photoreception and magnetoreception in some animals. Neurophysiological studies have the potential to prove this link and identify the location of and the mechanism underlying the magnetoreception system.

Introduction

The sensitivity of animals to the geomagnetic field has proven to be one of the most interesting and lasting challenges in sensory biology. The use of magnetic cues for spatial orientation has been found in a taxonomically diverse array of animals (Wiltschko and Wiltschko, 1995). Nevertheless, neither the physiological mechanism nor the morphological structure(s) underlying this ability have been identified conclusively.

Studies to date have identified functional characteristics of animal magnetoreception (see Lohmann and Johnsen, 2000). Orientation responses to magnetic cues of newts, birds, and fruit flies were shown to be dependent on the wavelength of light (Phillips and Borland, 1992; Phillips and Sayeed, 1993; Wiltschko et al., 1993, 2000; Deutschlander et al., 1999a, 1999b; Wiltschko and Wiltschko, 2001), while those of mole rats, sea turtles, and mealworm beetles appear to be independent of light (see Wiltschko and Wiltschko, 1995). Two functional modes of animal magnetic compasses have been characterized: inclination and polarity compasses. Inclination compasses detect the angle of the field lines with the horizon, but cannot detect a reversal of the magnetic field polarity, as polarity compasses (e.g., a human navigator's compass) do. Birds and sea turtles have been shown to have an inclination, mole rats a polarity compass, and newts use either an inclination or a polarity compass depending on their orientation task. Why is it that despite a large mosaic of experimental findings, no clear picture has emerged yet as to how magnetoreception is accomplished?

One key challenge is that magnetic cues may serve as input for more than one sensory system and mediate more than one type of behavioral response, e.g., magnetic cues may provide an input to (1) an inclination compass, (2) a polarity compass, (3) a magnetic map (see below), as well as potentially (4) any of a variety of nonspecific influences. To identify the way in which magnetic cues are used requires a careful analysis of the animal's behavior. A recent study (Lohmann et al., 2001) exemplifies this approach. Hatchling loggerhead

sea turtles from Eastern Florida were exposed to three magnetic fields with varying intensities (31.0–49.1 μT) and inclinations (16.7°–59.3°). The choice of magnetic field stimuli was based on an extensive knowledge of the behavior of sea turtles. Hatchling sea turtles migrate the first years of their life, being carried by the currents of the North Atlantic gyre. At several points of their migration, bifurcating currents may carry turtles into unfavorable conditions, e.g., frigid arctic waters. The chosen magnetic field values correspond to values that would be encountered at these critical points. In all three cases, the turtles responded by swimming in a direction that would help them remain within the North Atlantic gyre.

The same experimental conditions could elicit very different responses from adult animals or from animals from populations living in other parts of the world (e.g., in the Indian Ocean) where geomagnetic field values differ. Extensive knowledge of an animal's behavior is thus necessary to identify sources of variation that otherwise may make it extremely difficult to obtain reproducible results. For example, the study by Lohmann et al. (2001) is the culmination of more than 10 years of work on the migratory orientation behavior of hatchling sea turtles.

The wealth of behavioral evidence for magnetic orientation has been the impetus for attempts to identify the brain centers involved in processing magnetic stimuli. Early neurophysiological studies provided evidence for magnetic sensitivity in several visual centers, namely the nucleus of the basal optic root (nBOR), the optic tectum, and the pineal gland (Semmler et al., 1984; Semmler and Demaine, 1986; Demaine and Semmler, 1985), although these results have proven, at times, difficult to reproduce (P. Semmler, personal communication). Rather than dismissing these early results, further neurophysiological studies are needed to identify and eliminate sources of variation. Such an effort is much easier to justify when several independent lines of evidence point to the same brain regions. We will review recent theoretical, behavioral, and neurophysiological studies emphasizing in each case the brain structures that are implicated in processing magnetic information.

Theory

Detection of an earth-strength, i.e., about 50 μT , magnetic field is a remarkably difficult technical task to be achieved solely with materials that are available in biological systems. Besides the use of a highly specialized electric sensor employed by elasmobranch fish, only two other possible magnetoreception systems have been shown to be sensitive to a 50 μT field in experiments: ferromagnetic materials and photoinduced radical pair processes. The ferromagnetic mechanism and its implications have been reviewed very recently (Kirschvink et al., 2001). In the present review, we focus on the predictions from the radical-pair mechanism.

The radical pair mechanism, proposed by Schulten et al. (1978), entails a biochemical electron transfer reaction generating radical pairs, in which anisotropic hyperfine interactions and external magnetic fields induce a

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change between the spin states of the radical products. These chemically different products can be modulated by the strength and direction of an external magnetic field, thus potentially providing the basis for a magnetic compass. Theoretical and experimental studies of modulation of radical pair reactions by magnetic fields of less than 100 μ T show that the radical pair mechanism is sensitive enough to provide a primary sensory mechanism for the geomagnetic field (Eveson et al., 2000).

The physics of the sensitivity of radical pair reactions to magnetic fields leads to several predictions about the characteristics of a radical pair-based compass system. Due to quantum mechanical symmetry properties valid for virtually all radical pairs, the angular dependence $F(\theta)$ of magnetic field effects obeys the symmetry relations: $F(\theta) = 90^\circ - F(\theta)$ and $F(\theta) = 180^\circ + F(\theta)$ (Ritz et al., 2000). A reversal of polarity, corresponding to a rotation by 180° , will therefore not change the magnetic field effects, i.e., the radical pair-based compass is intrinsically an inclination compass. A second characteristic is the complex influence of magnetic field strength on radical pair reactions. Changes in the strength of magnetic fields will influence the angular dependence as well as the size of magnetic field effects. Moreover, the size of magnetic field effects may decrease for an increase in magnetic field strength because of the competition between two different physical mechanisms underlying magnetic field effects on radical pairs (Ritz et al., 2000).

By far, the most common mechanism to generate a radical pair is through a photoinduced electron transfer reaction. Therefore, it is likely that photopigments are either part of the radical pair system or that they activate the radical pair system by excitation energy transfer. In order to be sensitive to the *direction* of the geomagnetic field, it is necessary for radical pairs to be fixed with respect to a geometric frame of reference. The radical pair mechanism thus requires an ordered array of radical pairs that involve or are linked to photopigments. One very promising lead involves cryptochromes, a class of recently discovered vertebrate photopigments that play a role in regulation of circadian rhythms. Both cryptochromes and the homologous photolyase enzymes utilize the flavin cofactor FADH as a pigment. FADH is highly redox active and upon photoactivation participates with other redox-active amino acids in the generation of a spin-polarized radical pair. Cryptochrome thus represents the first vertebrate photopigment that has been shown to generate (potentially magnetosensitive) radical pairs.

Additional links between photopigments and radical pair systems may be discovered in the future, leading to further candidate systems. The location of such linked photopigment/radical pair systems and the projections of such systems into brain areas offer a strong suggestion where to look for magnetosensitive brain centers. Cryptochrome expression has been found to occur in the inner nuclear and ganglion cell layers of the eye, which project into the nBOR, consistent with early neurophysiological findings (Semm et al., 1984).

Behavioral Studies

The influence of ambient light on magnetic compass orientation has been studied in several groups, including beetles, flies (*Drosophila*), amphibians, reptiles, birds, and mammals. Perhaps the most interesting finding

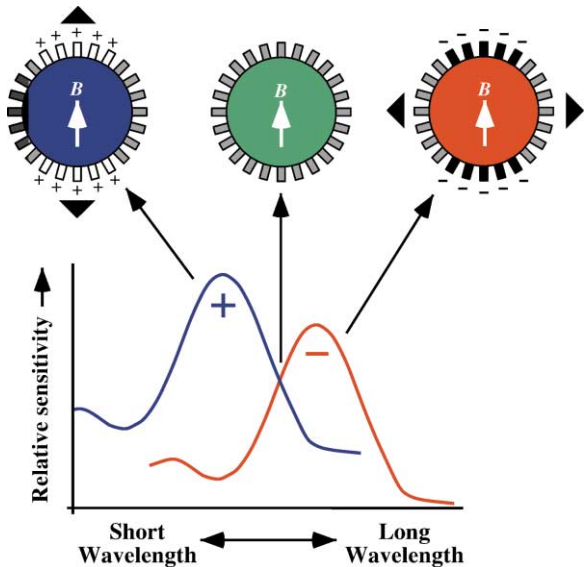


Figure 1. Antagonistic Receptor Model

Model of antagonistic interaction between a short wavelength (blue) and a long wavelength (red) receptor input, resulting in a 90° shift in axis of magnetic orientation (circles).

from these studies in the present context is the evidence for an $\sim 90^\circ$ shift in the direction of magnetic compass orientation under at least some intensities of long wavelength light (i.e., ≥ 500 nm), e.g., in *Drosophila melanogaster* (Phillips and Sayeed, 1993), in Eastern red-spotted newt *Notophthalmus viridescens* (Phillips and Borland, 1992; Deutschlander et al., 1999a, 1999b), in Tasmanian silveryeyes *Zosterops l. lateralis* (Wiltschko et al., 2000), and in European robins *Erithacus rubecola* (Wiltschko and Wiltschko, 2001). In newts, the behavioral results suggest that the wavelength dependence of magnetic compass orientation results from a direct effect of light on the underlying magnetoreception mechanism (Phillips and Borland, 1992; Deutschlander et al., 1999a).

The 90° shift in newts can be explained by an antagonistic interaction between a short wavelength (≤ 450 nm) and a less sensitive long wavelength (≥ 500 nm) input (Figure 1). In this model, intermediate wavelengths that excite the two inputs more or less equally should cause the complementary patterns to cancel out (Figure 1, green circle). Consistent with this prediction, newts tested under 475 nm light failed to show a consistent direction of orientation relative to the magnetic field (Phillips and Borland, 1992).

The model shown in Figure 1 provides a "fingerprint" that can be used to identify regions of the brain that are involved in processing of magnetic information. But where should this search begin? Dodt and Heerd (1966) identified units in the frontal organ of frogs (an outgrowth of the pineal that is homologous to the parapineal lobe of the pineal in salamanders) that receive antagonistic spectral inputs that closely match those proposed by the antagonistic model shown in Figure 1. Behavioral experiments with newts in which small spectral "caps" were attached to the top of the head to selectively alter wavelengths of light reaching the pineal suggest that

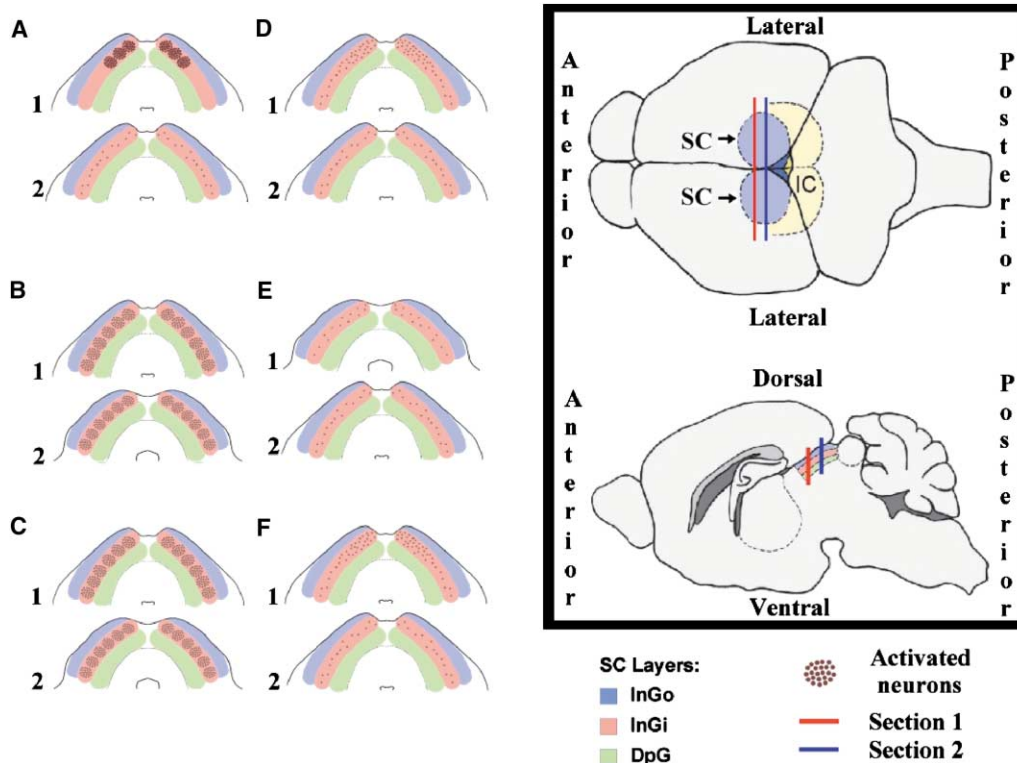


Figure 2. Magnetically Stimulated Activation in Mole Rat Brain

Variation of c-Fos expression in the superior colliculus (SC) of mole rats exposed to experimental conditions A–F as indicated below (Nemec et al., 2001).

- (A) Static field ($mN = 0^\circ$): Novel circular arena
- (B) Field shift ($mN = 0^\circ \longleftrightarrow mN = 240^\circ$) every 5 min: Novel circular arena
- (C) Field shift ($mN = 0^\circ \longleftrightarrow mN = 240^\circ$) every 1 s: Novel circular arena
- (D) Cancelled field (shielded room): Novel circular arena
- (E) Static field ($mN = 0^\circ$): Familiar home cage
- (F) Cancelled field (shielded room): Familiar home cage

short wavelength and long wavelength inputs to the magnetic compass are, in fact, located in or near the pineal (Deutschlander et al., 1999b; Phillips et al., 2001). The pineal complex of amphibians also has been shown to mediate compass orientation using the sun and the E vector of plane-polarized light, the latter requiring an ordered array of light-absorbing molecules. Thus, the pineal is an excellent candidate for the site of the light-dependent magnetic compass in amphibians.

In birds, magnetic compass orientation exhibits a complex dependence on wavelength and intensity of light (Wiltschko et al., 1993, 2000; Wiltschko and Wiltschko, 2001). To date, it has not been possible to carry out experiments comparable to those in newts to determine if the wavelength-dependent shifts in the direction of orientation result from a direct effect on the magnetic compass. Given the neurophysiological findings of Semm and colleagues (earlier references), however, such a possibility seems likely. Also less clear than in the case of newts is the location of the magnetic compass in birds. Neurophysiological experiments have provided evidence for magnetic field sensitivity in the avian pineal (Demaine and Semm, 1985), but it does not appear to be the primary site of the magnetic compass in birds, suggesting rather an involvement of the eyes (see Wiltschko and Wiltschko, 1995).

Neuroanatomy

Behavioral studies have shown that Zambian mole rats (*Cryptomys anelli*) placed in unfamiliar arenas use magnetic information to select the location of a nest in a novel arena (Marhold et al., 1997). Recently, Nemec et al. (2001) combined this well-characterized behavioral response with a technique for detecting patterns of neural activation in the brain, i.e., early gene expression of the transcriptional regulatory protein c-Fos. After exposing mole rats to varying environments and magnetic field conditions (see Figure 2), c-Fos expression in various brain areas was monitored by an immunocytochemical staining technique.

Variation in density and relative distribution of c-Fos expression was found in different areas within the superior colliculus (SC; Figure 2). In particular, a strong increase in c-Fos expression was apparent in the intermediate gray layer (InGi) for animals exposed to an earth-strength magnetic field in a novel environment (A). A more widely dispersed increase in c-Fos expression was found in the InGi of mole rats exposed to periodic changes in the azimuth of the magnetic field in the circular arena (B and C). Control conditions show that neither novelty of the environment (D) nor a static magnetic field alone (E) elicit an increase in c-Fos expression. Since the SC is a center for integration of multimodal sensory informa-

tion, further studies using more extensive control conditions are warranted to rule out the possibility that input from other sensory modalities (visual, auditory, somatosensory) instead of magnetic input is responsible for the increase in c-Fos expression. Nevertheless, the findings presented by Nemec et al. (2001) suggest strongly that the SC is involved in processing magnetic information. In fact, the SC is a likely site for the integration of magnetic information with other spatial information since it plays an important role in coupling multimodal sensory information to directed motor output. The evidence for the SC's involvement in processing magnetic information in a mammal lends credibility to the earlier reports of magnetic sensitivity in the homologous optic tectum of birds.

Summary

Theoretical considerations, behavioral observations, and neurophysiological recordings have led us independently to three brain structures involved in processing magnetic information, namely (1) the pineal gland, a possible site of light-dependent magnetoreception in amphibians and birds, (2) the optic tectum and homologous superior colliculus in birds and mammals, which appear to be involved in processing both light-independent (mole rats) and light-dependent (birds) magnetic information, and (3) the nBOR, a site which possibly couples inputs from magnetosensitive photopigments in the eye to vestibular inputs. The convergence of evidence, albeit at times circumstantial, from such different approaches suggests that these brain areas indeed play a role in magnetoreception. A fourth region of the brain that has been implicated in magnetite-based magnetoreception is the trigeminal nerve system, as discussed in Kirschvink et al. (2001).

Techniques that are new to this area of research, like those used by Nemec et al. (2001), can be used to obtain independent assessments of the involvement of structures that have been implicated in the detection or processing of magnetic information. The time is right for neuroscientists to turn their attention again to characterizing the physiological, molecular, and biophysical basis of the magnetic sense(s) using the insights from behavioral biology and theoretical biophysics. Most productive of all are likely to be truly interdisciplinary collaborations combining behavioral, genetic, neurophysiological, and biophysical approaches.

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